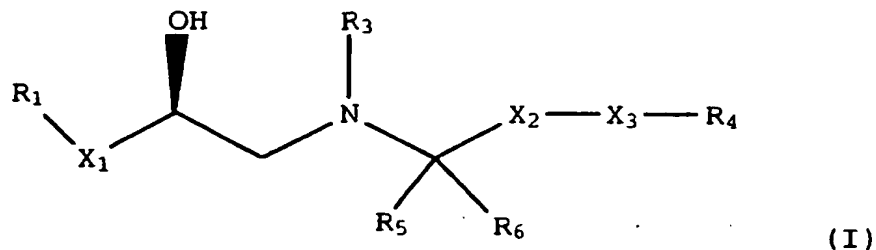


-109-

We claim:

1. A method of stimulating the β_3 receptor which comprises administering to a patient in need thereof a compound of Formula I:



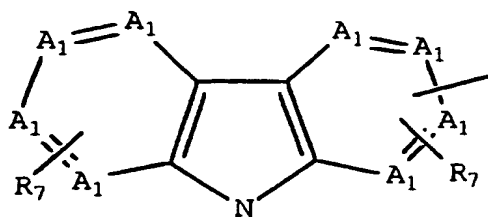
wherein:

X1 is -OCH₂-, -SCH₂-, or a bond;

10 X2 is a bond, or a 1 to 5 carbon straight or branched alkylene;

X3 is O, S, or a bond;

R1 is a fused heterocycle of the formula:



15

the A₁ groups are independently carbon or nitrogen, provided that no more than 2 nitrogens may be contained in either fused 6 membered ring and those 2 nitrogens may not be adjacent;

20

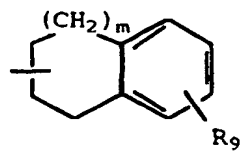
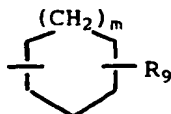
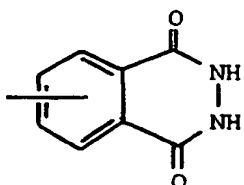
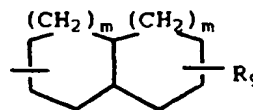
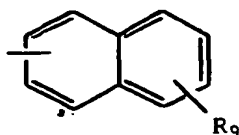
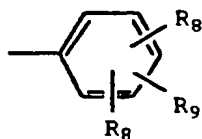
R₂ is independently hydrogen, C₁-C₄ alkyl, or aryl;

R₃ is hydrogen or C₁-C₄ alkyl;

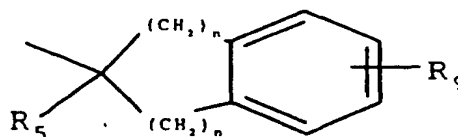
R₄ is an optionally substituted heterocycle or a moiety selected from the group consisting of:

25

-110-



- R5 is hydrogen or C1-C4 alkyl;
 R6 is hydrogen, C1-C4 alkyl, or CO₂(C1-C4 alkyl);
 5 or R5 and R6 combine with the carbon to which each
 is attached to form a C3-C6 cycloalkyl;
 or R6 combines with X₂ and the carbon to which
 each is attached to form a C3-C8 cycloalkyl;
 or R6 combines with X₂, R₄, and the carbon to
 10 which each is attached to form:



- provided that R₅ is hydrogen;
 R₇ is independently hydrogen, halo, hydroxy, OR₂,
 15 C1-C4 alkyl, C1-C4 haloalkyl, aryl, COOR₂, CONR₂R₂, NHCOR₂,
 C1-C4 alkoxy, NHR₂, SR₂, CN, SO₂R₂, SO₂NHR₂, or SOR₂;
 R₈ is independently hydrogen, halo, or C1-C4
 alkyl;
 R₉ is hydrogen, halo, hydroxy, CN, OR₁₀, C1-C4
 20 alkyl, C1-C4 haloalkyl, CO₂R₂, CONR₁₁R₁₂, CONH(C1-C4 alkyl
 or C1-C4 alkoxy), SR₂, CSNR₂, CSNR₁₁R₁₂, NR₂SO₂R₂, SO₂R₂,
 SO₂NR₁₁R₁₂, SOR₂, NR₁₁R₁₂, optionally substituted aryl,
 optionally substituted heterocycle, or C2-C4 alkenyl
 substituted with CN, CO₂R₂ or CONR₁₁R₁₂;

-111-

R₁₀ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, (CH₂)_nC₃-C₈ cycloalkyl, (CH₂)_naryl, (CH₂)_nheterocycle, (CH₂)_nC₃-C₈ optionally substituted cycloalkyl, (CH₂)_n optionally substituted aryl, (CH₂)_n optionally substituted heterocycle,
 5 or (CH₂)_nCO₂R₂;

R₁₁ and R₁₂ are independently hydrogen, C₁-C₄ alkyl, aryl, (CH₂)_naryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

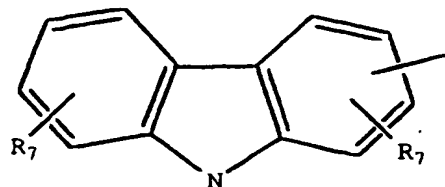
10 m is 0 or 1;

n is independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

2. The method of Claim 1 wherein R₁ is

15



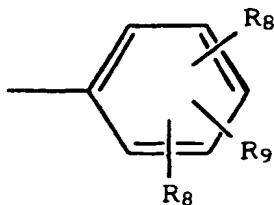
3. The method of Claim 2 wherein R₇ is hydrogen and R₃ is hydrogen.

20

4. The method of Claim 3 wherein X₃ is O or a bond.

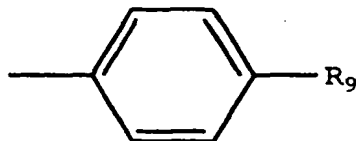
5. The method of Claim 4 wherein R₅ and R₆ are
 25 methyl, X₂ is methylene or ethylene, and X₃ is a bond.

6. The method of Claim 5 wherein R₄ is



-112-

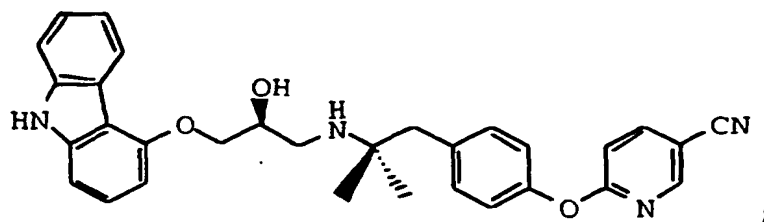
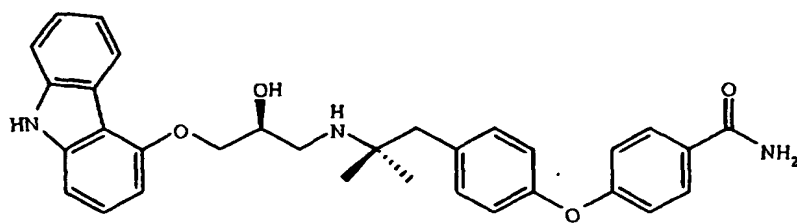
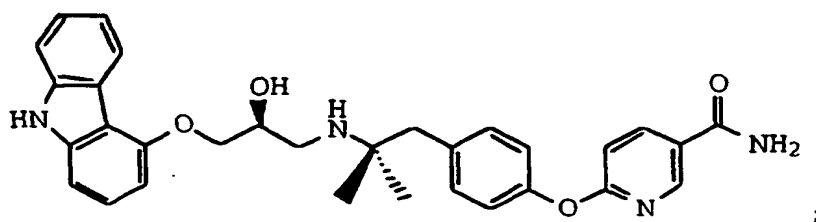
7. The method of Claim 6 wherein R_4 is



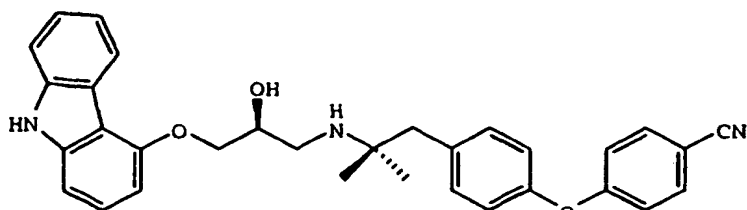
5 and R_9 is OR_{10} or $NR_2SO_2R_2$.

8. The method of Claim 7 wherein R_{10} is phenyl or pyridyl said phenyl or pyridyl being substituted with CN, hydroxy, $CONR_{11}R_{12}$, CO_2R_2 , SO_2R_2 , or $SO_2NR_{11}R_{12}$.

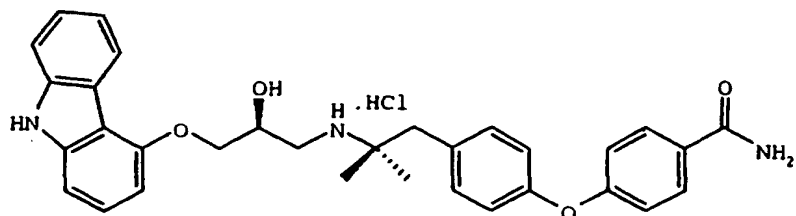
9. The method of Claim 8 wherein the compound is:



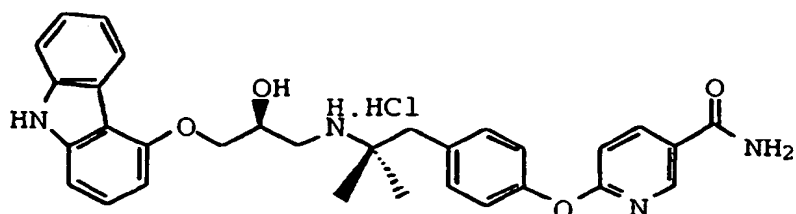
-113-



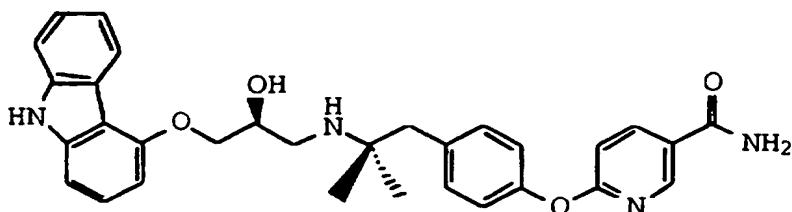
or a pharmaceutically acceptable salt or solvate thereof; or



; or

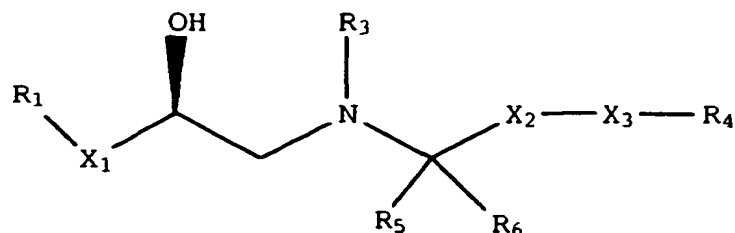


10. The method of claim 9 wherein the compound is



10 or a pharmaceutically acceptable salt or solvate.

11. A method of treating obesity which comprises administering to a patient in need thereof a compound of Formula I:



(I)

wherein:

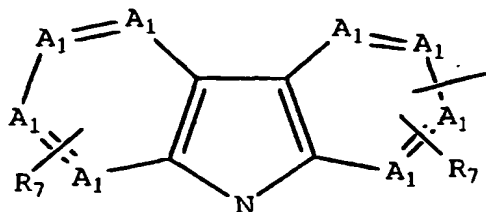
-114-

X₁ is -OCH₂-, -SCH₂-, or a bond;

X₂ is a bond, or a 1 to 5 carbon straight or branched alkylene;

X₃ is O, S, or a bond;

5 R₁ is a fused heterocycle of the formula:

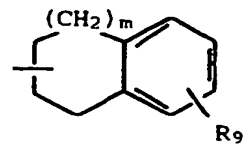
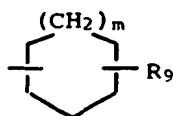
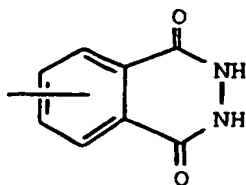
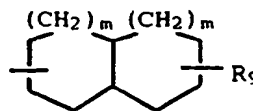
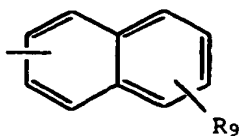
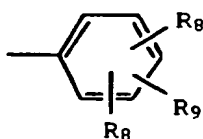


10 the A₁ groups are independently carbon or nitrogen, provided that no more than 2 nitrogens may be contained in either fused 6 membered ring and those 2 nitrogens may not be adjacent;

R₂ is independently hydrogen, C₁-C₄ alkyl, or aryl;

15 R₃ is hydrogen or C₁-C₄ alkyl;

R₄ is an optionally substituted heterocycle or a moiety selected from the group consisting of:



20

R₅ is hydrogen or C₁-C₄ alkyl;

R₆ is hydrogen, C₁-C₄ alkyl, or CO₂(C₁-C₄ alkyl);

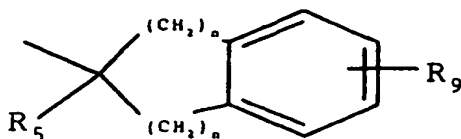
or R₅ and R₆ combine with the carbon to which each is attached to form a C₃-C₆ cycloalkyl;

-115-

or R₆ combines with X₂ and the carbon to which each is attached to form a C₃-C₈ cycloalkyl;

or R₆ combines with X₂, R₄, and the carbon to which each is attached to form:

5



provided that R₅ is hydrogen;

R₇ is independently hydrogen, halo, hydroxy, OR₂, C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl, COOR₂, CONR₂R₂, NHCOR₂,
 10 C₁-C₄ alkoxy, NHR₂, SR₂, CN, SO₂R₂, SO₂NHR₂, or SOR₂;

R₈ is independently hydrogen, halo, or C₁-C₄ alkyl;

R₉ is hydrogen, halo, hydroxy, CN, OR₁₀, C₁-C₄ alkyl, C₁-C₄ haloalkyl, CO₂R₂, CONR₁₁R₁₂, CONH(C₁-C₄ alkyl
 15 or C₁-C₄ alkoxy), SR₂, CSNR₂, CSNR₁₁R₁₂, NR₂SO₂R₂, SO₂R₂, SO₂NR₁₁R₁₂, SOR₂, NR₁₁R₁₂, optionally substituted aryl, optionally substituted heterocycle, or C₂-C₄ alkenyl substituted with CN, CO₂R₂ or CONR₁₁R₁₂;

R₁₀ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, (CH₂)_nC₃-C₈ cycloalkyl, (CH₂)_naryl, (CH₂)_nheterocycle, (CH₂)_nC₃-C₈ optionally substituted cycloalkyl, (CH₂)_n optionally substituted aryl, (CH₂)_n optionally substituted heterocycle, or (CH₂)_nCO₂R₂;

R₁₁ and R₁₂ are independently hydrogen, C₁-C₄ alkyl, aryl, (CH₂)_naryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

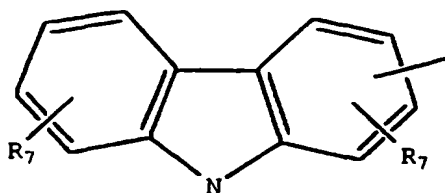
m is 0 or 1;

n is independently 0, 1, 2, or 3;

30 or a pharmaceutically acceptable salt or solvate thereof.

12. The method of Claim 11 wherein R₁ is

-116-



13. The method of Claim 12 wherein R₇ is hydrogen and R₃ is hydrogen.

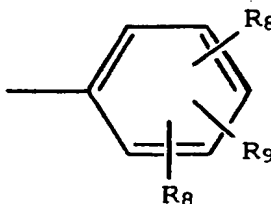
5

14. The method of Claim 13 wherein X₃ is O or a bond.

15. The method of Claim 14 wherein R₅ and R₆ are methyl, X₂ is methylene or ethylene, and X₃ is a bond.

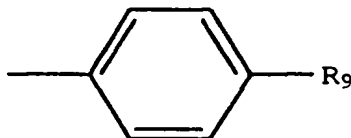
10

16. The method of Claim 15 wherein R₄ is



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17. The method of Claim 16 wherein R₄ is



and R₉ is OR₁₀ or NR₂SO₂R₂.

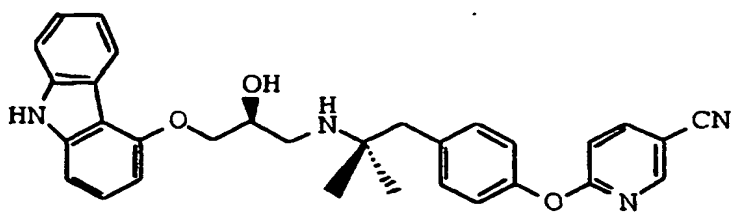
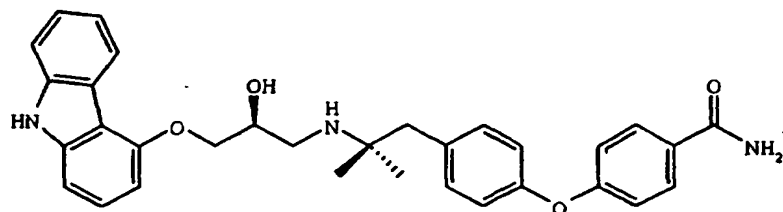
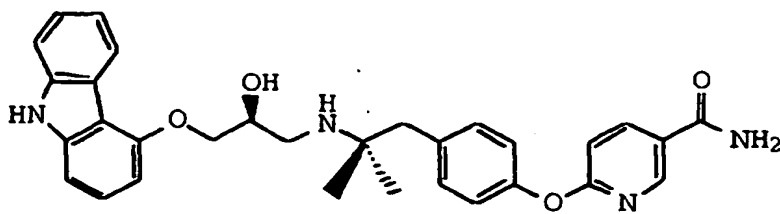
20

18. The method of Claim 17 wherein R₁₀ is phenyl or pyridyl said phenyl or pyridyl being substituted with CN, hydroxy, CONR₁₁R₁₂, CO₂R₂, SO₂R₂, or SO₂NR₁₁R₁₂.

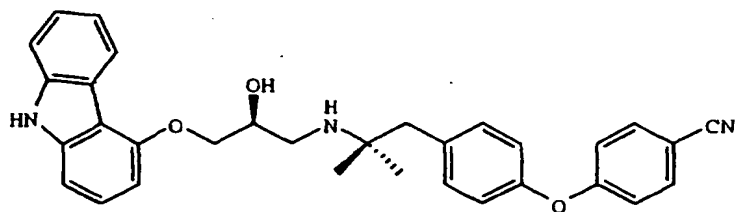
25

19. The method of Claim 18 wherein the compound is:

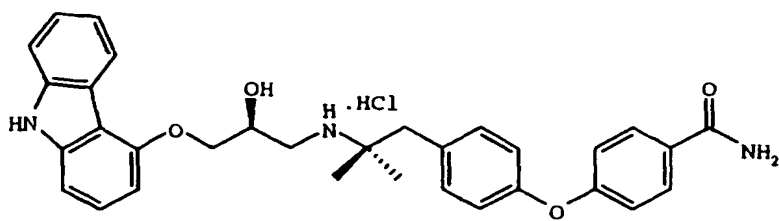
-117-



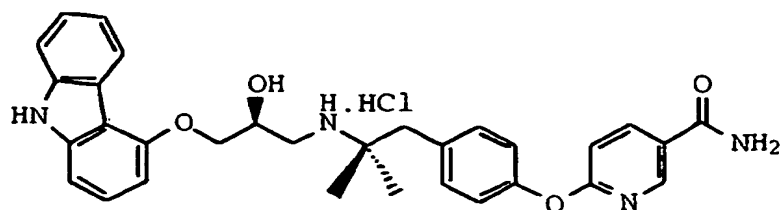
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or a pharmaceutically acceptable salt or solvate thereof; or



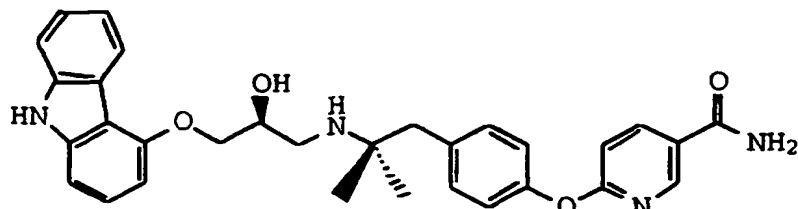
10



; or

-118-

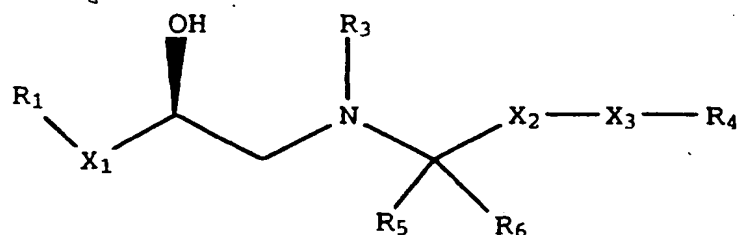
20. The method of claim 19 wherein the compound is



or a pharmaceutically acceptable salt or solvate thereof.

5

21. A method of treating Type II diabetes which comprises administering to a patient in need thereof a compound of Formula I:



(I)

10

wherein:

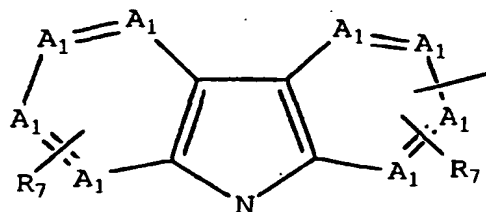
X₁ is -OCH₂-, -SCH₂-, or a bond;

X₂ is a bond, or a 1 to 5 carbon straight or branched alkylene;

15

X₃ is O, S, or a bond;

R₁ is a fused heterocycle of the formula:



20

the A₁ groups are independently carbon or nitrogen, provided that no more than 2 nitrogens may be contained in either fused 6 membered ring and those 2 nitrogens may not be adjacent;

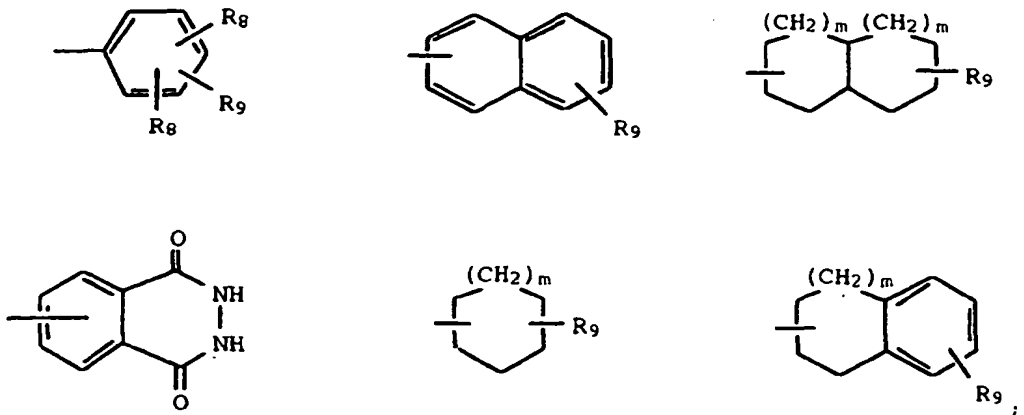
25

R₂ is independently hydrogen, C₁-C₄ alkyl, or aryl;

R₃ is hydrogen or C₁-C₄ alkyl;

-119-

R₄ is an optionally substituted heterocycle or a moiety selected from the group consisting of:



5

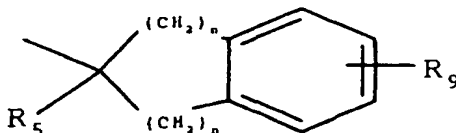
R₅ is hydrogen or C₁-C₄ alkyl;

R₆ is hydrogen, C₁-C₄ alkyl, or CO₂(C₁-C₄ alkyl);

or R₅ and R₆ combine with the carbon to which each is attached to form a C₃-C₆ cycloalkyl;

10 or R₆ combines with X₂ and the carbon to which each is attached to form a C₃-C₈ cycloalkyl;

or R₆ combines with X₂, R₄, and the carbon to which each is attached to form:



15

provided that R₅ is hydrogen;

R₇ is independently hydrogen, halo, hydroxy, OR₂, C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl, COOR₂, CONR₂R₂, NHCOR₂, C₁-C₄ alkoxy, NHR₂, SR₂, CN, SO₂R₂, SO₂NHR₂, or SOR₂;

20 R₈ is independently hydrogen, halo, or C₁-C₄ alkyl;

R₉ is hydrogen, halo, hydroxy, CN, OR₁₀, C₁-C₄ alkyl, C₁-C₄ haloalkyl, CO₂R₂, CONR₁₁R₁₂, CONH(C₁-C₄ alkyl or C₁-C₄ alkoxy), SR₂, CSNR₂, CSNR₁₁R₁₂, NR₂SO₂R₂, SO₂R₂,
25 SO₂NR₁₁R₁₂, SOR₂, NR₁₁R₁₂, optionally substituted aryl,

- 120 -

optionally substituted heterocycle, or C₂-C₄ alkenyl substituted with CN, CO₂R₂ or CONR₁₁R₁₂;

R₁₀ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, (CH₂)_nC₃-C₈ cycloalkyl, (CH₂)_naryl, (CH₂)_nheterocycle, (CH₂)_nC₃-C₈ optionally substituted cycloalkyl, (CH₂)_n optionally substituted aryl, (CH₂)_n optionally substituted heterocycle, or (CH₂)_nCO₂R₂;

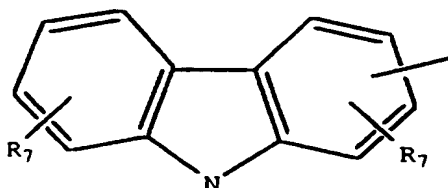
R₁₁ and R₁₂ are independently hydrogen, C₁-C₄ alkyl, aryl, (CH₂)_naryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

m is 0 or 1;

n is independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

22. The method of Claim 21 wherein R₁ is



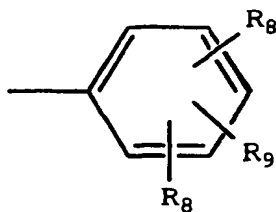
23. The method of Claim 22 wherein R₇ is hydrogen and R₃ is hydrogen.

24. The method of Claim 23 wherein X₃ is O or a bond.

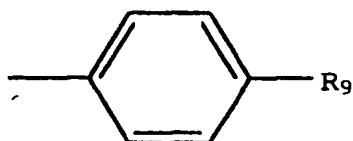
25. The method of Claim 24 wherein R₅ and R₆ are methyl, X₂ is methylene or ethylene, and X₃ is a bond.

26. The method of Claim 25 wherein R₄ is

-121-



27. The method of Claim 26 wherein R_4 is



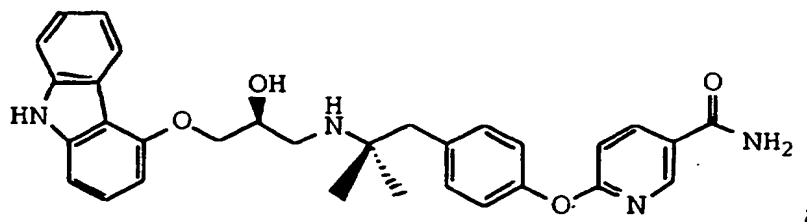
5

and R_9 is OR_{10} or $NR_2SO_2R_2$.

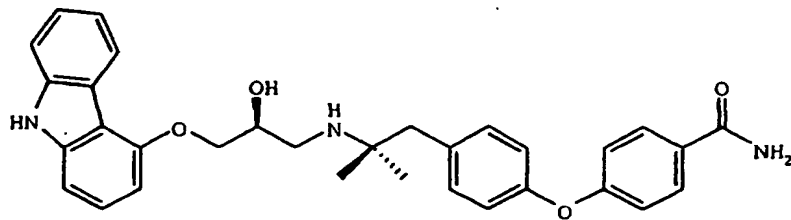
28. The method of Claim 27 wherein R_{10} is phenyl or pyridyl said phenyl or pyridyl being substituted with CN, hydroxy, $CONR_{11}R_{12}$, CO_2R_2 , SO_2R_2 , or $SO_2NR_{11}R_{12}$.

10

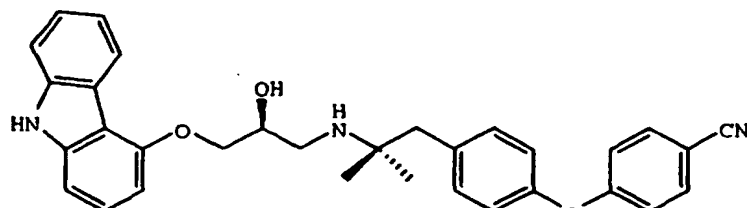
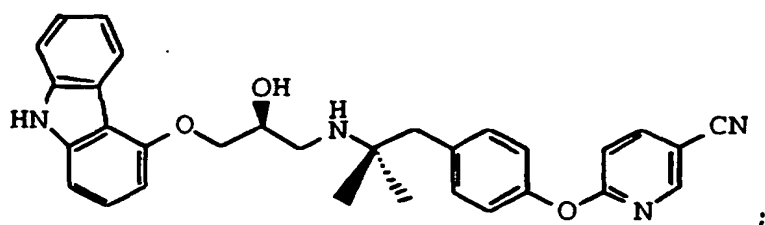
29. The method of Claim 28 wherein the compound is:



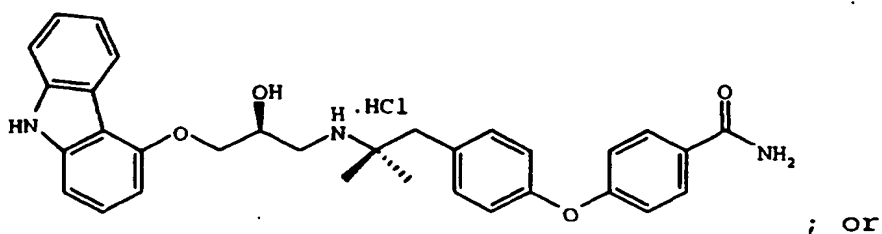
15



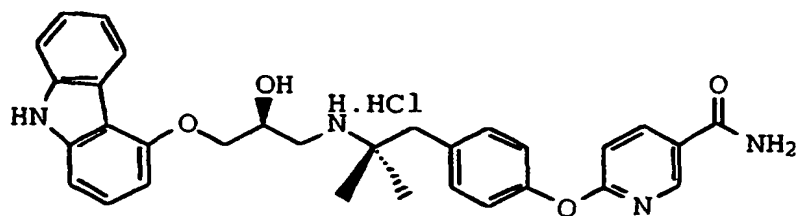
-122-



or a pharmaceutically acceptable salt or solvate thereof; or

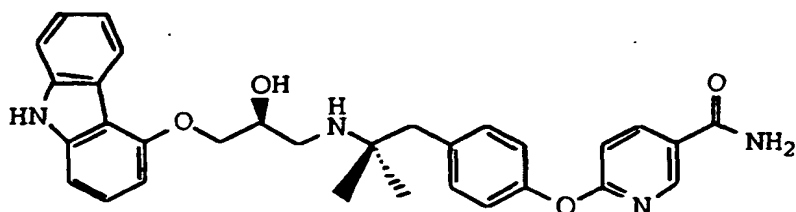


; or



10

30. The method of claim 29 wherein the compound is

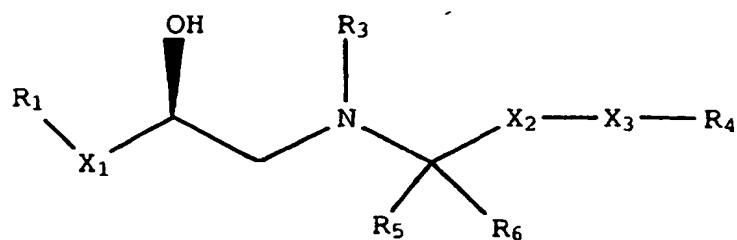


or a pharmaceutically acceptable salt or solvate.

15

31. A compound of the Formula II

-123-

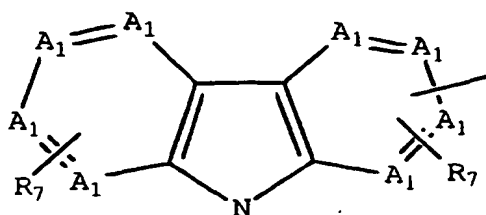


wherein:

X₁ is -OCH₂-, -SCH₂-, or a bond;

X₃ is O, S, or a bond;

5 R₁ is a fused heterocycle of the formula:



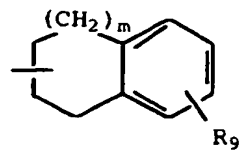
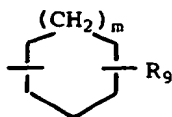
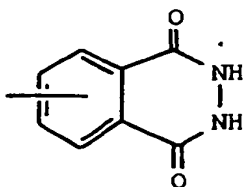
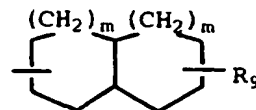
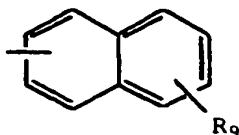
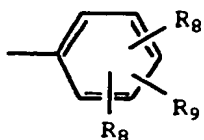
the A₁ groups of said heterocycle are

10 independently carbon or nitrogen, provided that no more than 2 nitrogens may be contained in either fused 6 membered ring and those 2 nitrogens may not be adjacent;

R₂ is independently hydrogen, C₁-C₄ alkyl, or aryl;

15 R₃ is hydrogen or C₁-C₄ alkyl;

R₄ is an optionally substituted heterocycle or a moiety selected from the group consisting of:



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X₂ is a bond, or a 1 to 5 carbon straight or branched alkylene;

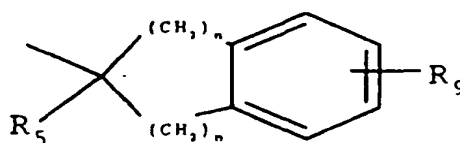
R₅ is hydrogen or C₁-C₄ alkyl;

R₆ is hydrogen, C₁-C₄ alkyl, or CO₂(C₁-C₄ alkyl);

5 or R₅ and R₆ combine with the carbon to which each is attached to form a C₃-C₆ cycloalkyl;

or R₆ combines with X₂ and the carbon to which each is attached to form a C₃-C₈ cycloalkyl;

10 or R₆ combines with X₂, R₄, and the carbon to which each is attached to form:



provided that R₅ is hydrogen;

15 R₇ is independently hydrogen, halo, hydroxy, OR₂, C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl, COOR₂, CONHR₂, NHCOR₂, C₁-C₄ alkoxy, NHR₂, SR₂, CN, SO₂R₂, SO₂NHR₂, or SOR₂;

R₈ is independently hydrogen, halo or C₁-C₄ alkyl;

20 R₉ is halo, CN, OR₁₀, C₁-C₄ alkyl, C₁-C₄ haloalkyl, CO₂R₂, CONR₁₁R₁₂, CONH(C₁-C₄ alkyl or C₁-C₄ alkoxy), SR₂, CSNR₂, CSNR₁₁R₁₂, NR₂SO₂R₂, SO₂R₂, SO₂NR₁₁R₁₂, SOR₂, NR₁₁R₁₂, optionally substituted aryl, optionally substituted heterocycle, or C₂-C₄ alkenyl substituted with CN, CO₂R₂ or CONR₁₁R₁₂;

25 R₁₀ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, (CH₂)_nC₃-C₈ cycloalkyl, (CH₂)_naryl, (CH₂)_nheterocycle, (CH₂)_nC₃-C₈ optionally substituted cycloalkyl, (CH₂)_n optionally substituted aryl, (CH₂)_n optionally substituted heterocycle, or (CH₂)_nCO₂R₂;

30 R₁₁ and R₁₂ are independently hydrogen, C₁-C₄ alkyl, aryl, (CH₂)_naryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

m is 0 or 1;

n is independently 0, 1, 2, or 3;

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provided:

when R₅ or R₆ is hydrogen; either1) one or more A₁ must be nitrogen,

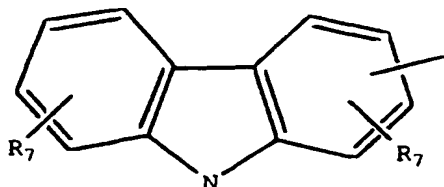
or

- 5 2) R₉ is CN, OR₁₀, CO₂R₂, CSNR₂, CSNR₁₁R₁₂,
NR₂SO₂R₂, SO₂NR₁₁R₁₂, optionally substituted aryl,
optionally substituted heterocycle, or C₂-C₄ alkenyl
substituted with CN, CO₂R₂ or CONR₁₁R₁₂; and

- 10 R₁₀ is C₁-C₄ haloalkyl, (CH₂)_nC₃-C₈ cycloalkyl,
(CH₂)_nheterocycle, (CH₂)_nC₃-C₈ optionally substituted
cycloalkyl, (CH₂)_n optionally substituted aryl, or (CH₂)_n
optionally substituted heterocycle;
or a pharmaceutically acceptable salt or solvate thereof.

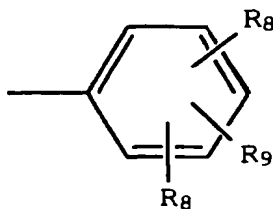
- 15 32. A compound of Claim 31 wherein R₅ and R₆ are
methyl or ethyl.

33. A compound of Claim 32 wherein R₁ is



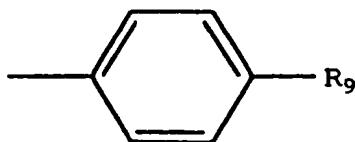
34. A compound of Claim 33 wherein X₂ is
methylene or ethylene.

- 25 35. A compound of Claim 34 wherein R₄ is



36. A compound of Claim 35 wherein R₄ is

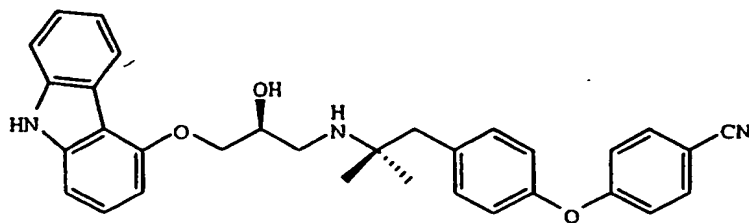
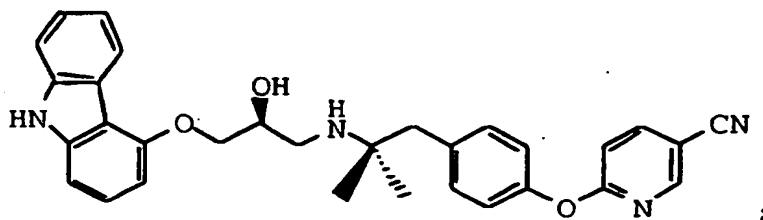
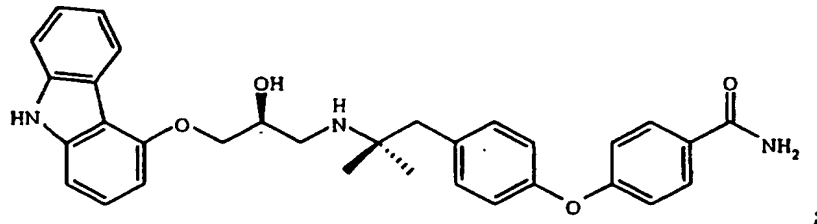
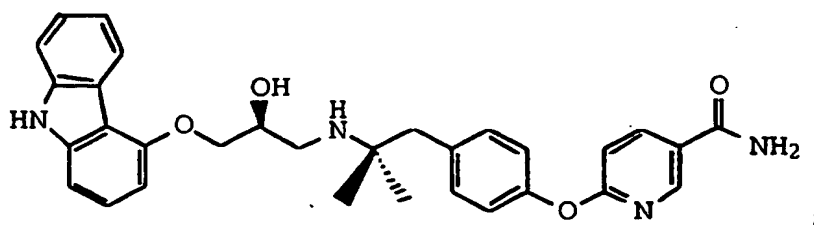
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and R_9 is OR_{10} or $NR_2SO_2R_2$.

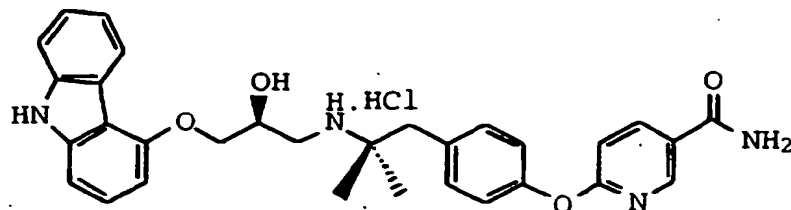
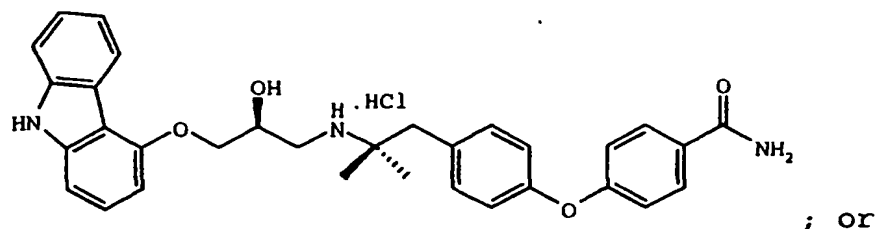
- 5 37. A compound of Claim 36 wherein R_{10} is phenyl or pyridyl said phenyl or pyridyl being substituted with CN, $CONR_{11}R_{12}$, CO_2R_2 , SO_2R_2 , or $SO_2NR_{11}R_{12}$.

- 10 38. A compound of Claim 37 which is:

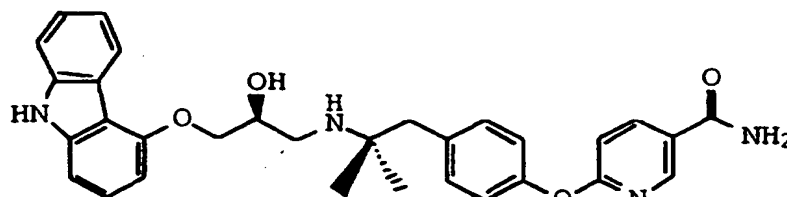


15 or a pharmaceutically acceptable salt or solvate thereof; or

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39. The compound of claim 38 of the formula



or a pharmaceutically acceptable salt or solvate.

40. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 31, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

41. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 32, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

42. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 33, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

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43. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 34, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

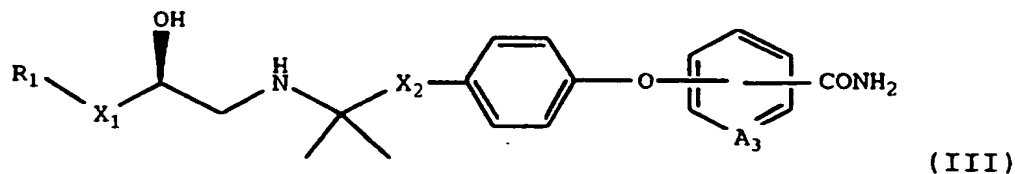
44. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 35, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

45. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 36, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

46. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 38, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

47. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 39, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

48. A process of preparing a compound of claim 31 of the formula III:



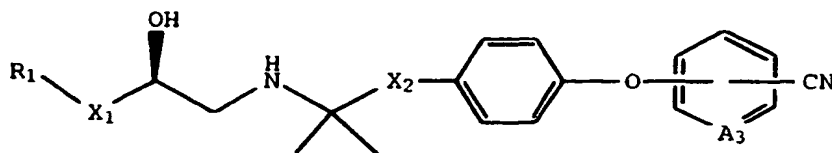
wherein:

A₃ is CH or N;

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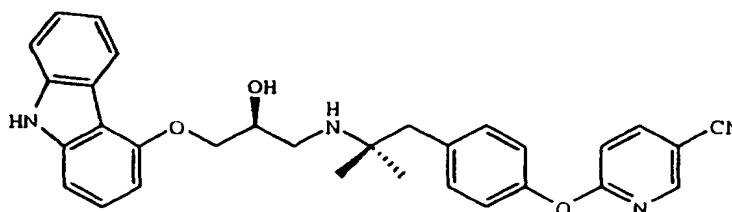
which comprises:

in step 1, hydrolysis of a compound of the formula:



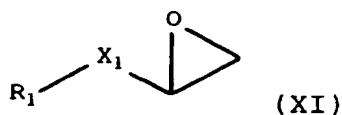
and optionally in step 2, reacting the product of step 1 with an acid to form an acid addition salt.

49. The process of claim 48 wherein in step 1 the hydrolysis is of a compound of the formula

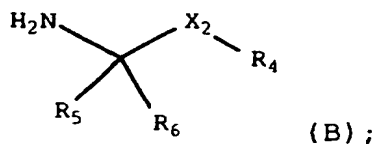


50. A process of preparing a compound of Claim 31, which comprises:

in step 1, reacting an epoxide of the formula XI:



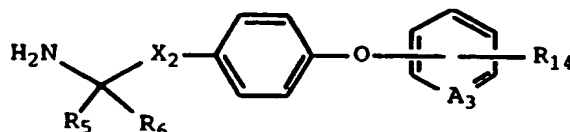
with an amine of formula B:



and optionally in step 2, reacting the product of step 1 with an acid to form an acid addition salt.

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51. A process of Claim 50, wherein the amine is of the formula:



wherein:

A₃ is CH or N;

R₁₄ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, COOR₂, CONR₁₁R₁₂, CONH(C₁-C₄ alkoxy), cyano, C₁-C₄ alkoxy, C₁-C₄ alkyl, phenyl, nitro, NR₁₁R₁₂, NHCO(C₁-C₄ alkyl), NHCO(benzyl), NHCO(phenyl), SR₂, S(C₁-C₄ alkyl), OCO(C₁-C₄ alkyl), SO₂(NR₁₁R₁₂), SO₂(C₁-C₄ alkyl), or SO₂(phenyl).

52. The process of claim 50 wherein;

A₃ is N; and

R₁₄ is COOR₂, CONR₁₁R₁₂, CONH(C₁-C₄ alkoxy), or cyano.